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Clinical Pharmacology of Pivampicillin

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Studies on pivampicillin hydrochloride and ampicillin trihydrate, administered in capsules to healthy volunteers, indicated that pivampicillin was absorbed more efficiently from the gastrointestinal tract than ampicillin. Average peak concentrations of ampicillin in the serum after doses equimolar to 250 mg of ampicillin were 6.8 μg/ml at 56 min with pivampicillin and 1.96 μg/ml at 1 h 24 min with ampicillin. The maximal concentration after pivampicillin treatment was also higher than that recorded when twice the equimolar dose of ampicillin, which averaged 3.2 μg/ml at 1 h 42 min, was used. The urinary excretion of ampicillin, expressed as a percentage of the administered dose, averaged 67 to 73 and 25 to 29% after administration of pivampicillin and ampicillin, respectively. The bioavailability of ampicillin, taken as the area under the serum curve, obtained with pivampicillin at a 250-mg ampicillin dose level was superior to that obtained with a 500-mg dose of ampicillin. Comparison of a suspension intended for children, containing the pivampicillin free base with a suspension of ampicillin trihydrate, emphasized the difference recorded for the capsule preparations. Administration of pivampicillin with a meal rich in fat and protein had no depressant effect on the absorption. Concurrent administration of probenecid caused higher and prolonged concentrations of ampicillin in the serum.

Although the introduction of ampicillin in 1961 (1, 19, 22, 23) constituted a major advance in systemic chemotherapy by extending the advantages of the penicillins to gram-negative organisms, ampicillin therapy has suffered from the disadvantage of incomplete absorption from the gastrointestinal tract, only about 25 to 30% of the orally administered ampicillin being recovered in urine (11, 13). This problem has recently been overcome by the development of pivampicillin (3). The drug, a pivaloyloxymethyl ester of ampicillin, is rapidly and completely hydrolyzed to ampicillin in the body, and the antibiotic activity of the compound is thus attributable to ampicillin (3, 4). Pivampicillin is normally used in the easily soluble hydrochloride form. It has been shown that much higher blood and urine concentrations of ampicillin are achieved after oral administration of pivampicillin than with equimolar amounts of oral ampicillin (4, 7, 8, 10). The fact that serum and urine levels after oral pivampicillin administration are comparable with those obtained after intramuscular administration of an equimolar amount of ampicillin indicates a practically complete absorption of pivampicillin from the gastrointestinal tract (10). The superior absorption of oral pivampicillin has also been shown in many other comparative studies (2, 6, 9, 15, 16). In studies evaluating the effect of the absorptive state, it has repeatedly been shown that food has no depressant action on the absorption of pivampicillin (3, 7, 10). In contrast, Fernandez et al. (6) and Magni and Sjövall concluded that the effect is similar to that observed for ampicillin (15).

This paper describes investigations undertaken to compare the absorption of pivampicillin with that of ampicillin, and to study the effect of food consumption on the absorption of pivampicillin.

Higher and more prolonged serum levels after administration of ampicillin have been obtained by concurrent administration of probenecid (12, 17, 18), but only one previous publication has mentioned a similar effect of probenecid on the serum levels after pivampicillin administration (21). The results of the investigation of the serum levels and urinary excretion of ampicillin after pivampicillin was administered concurrently with probenecid is included in this paper. In addition to these studies performed with dosage forms intended for adults, a suspension of ampicillin suitable for children has been compared with an oral suspension of pivampicillin that has been developed recently to fulfill the need for a liquid form of this compound, and that has proven useful in pediatric practice (21). This suspension has been formulated with the free pivampicillin

TABLE 1. *Serum concentrations and urinary excretion of ampicillin after oral administration of single doses of pivampicillin hydrochloride (equimolar to 250 mg of ampicillin) to healthy volunteers in the fasting state or immediately after a meal*

Absorptive state	Serum concn (μg/ml)								Urinary excretion[a] (% of dose)
	0.25[b]	0.5	1	1.5	2	3	4	6	
Fasting	0.70	3.0	4.7	5.0	4.1	2.7	1.1	0.38	63
	0.50	5.2	8.9	6.0	3.3	1.4	0.62	0.17	95
	<0.03	1.8	4.4	8.4	5.4	2.0	1.0	0.33	70
	6.4	9.8	5.0	3.3	2.2	1.1	0.49	0.16	57
	0.03	2.3	6.1	6.6	n.d.	1.7	0.72	0.23	83
	0.46	2.7	4.0	5.0	3.2	1.5	0.64	0.19	57
	1.6	2.9	4.6	5.8	3.9	1.5	0.66	0.22	77
	0.61	6.7	8.9	4.4	2.3	0.96	0.50	0.16	79
									Mean: 73
Postprandial	<0.03	0.28	6.7	8.0	6.2	3.0	1.3	0.33	63
	0.96	1.8	6.4	5.2	4.7	1.9	0.71	0.21	55
	0.08	1.7	4.9	4.4	4.7	2.1	1.5	0.29	68
	2.3	8.6	8.5	5.2	3.8	1.5	0.70	0.25	84
	0.04	1.3	3.9	4.1	3.8	2.9	0.96	0.30	80
	<0.03	1.7	5.0	4.2	3.8	2.0	0.72	0.17	71
	<0.03	<0.03	2.3	6.1	6.9	2.7	1.1	0.30	74
	<0.03	0.16	2.3	5.3	6.9	3.0	1.5	0.36	52
	<0.03	0.21	7.0	6.7	3.4	1.5	0.57	0.19	60
									Mean: 67

[a] 0 to 6 h after administration.
[b] Hours after administration.

base, which, in contrast to its hydrochloride salt, is sparingly soluble in water and, consequently, without a bitter taste.

MATERIALS AND METHODS

Pivampicillin was given as commercially available capsules containing the crystalline hydrochloride salt (Pondocillin, Leo Pharmaceutical Products) or as an aqueous suspension of the free pivampicillin base. Commercially available preparations of ampicillin trihydrate as capsules (Pentrexyl, Lundbeck) or a suspension suitable for children (Doktacillin, Astra) were used in comparative studies. Probenecid was administered as commercially available tablets (Probecid, Astra). The investigations were performed in healthy volunteers. One group, both fasting and nonfasting subjects, took part in the studies on the absorption of pivampicillin; the same group took part in those carried out for comparison with ampicillin. Another group was used for the comparative studies on oral suspensions of the two drugs; a third was used in the investigations of the effect of probenecid.

All volunteers were 30 to 50 years old, and their weights ranged from 60 to 80 kg. They received the drug either while they were fasting or immediately after a standard breakfast consisting of milk, bread and butter, cheese, eggs, and coffee. Two hours after the drug was administered, the subjects were allowed food ad libitum. Any medication was withheld for a minimum of 3 days prior to the studies. Blood samples were withdrawn from the antecubital vein at various times after the dosing, and complete urine collections were obtained. Serum was separated from the blood specimen by centrifugation, and both serum and urine samples were assayed microbiologically.

Antibiotic assay. Since pivampicillin is rapidly and completely hydrolyzed into ampicillin (3), the antibiotic activity in serum and urine was expressed as anhydrous ampicillin. The activity was assayed by the agar cup-plate technique with *Sarcina lutea* ATCC 9341 as the test organism and a standard preparation of ampicillin as the reference compound.

Calculation and graphical representation of results. The serum levels results presented in this paper are illustrated by curves generated by a computer on the basis of an empirically derived equation, $y = a + b/x + c \cdot x + d \cdot x^2$, that expresses the log of the serum concentration ($y = \log c$) as a function of time ($x = \sqrt{T - \phi}$). The method, developed by H. Engberg-Pedersen (5), provides curves fitted to the experimentally obtained serum data for each individual subject. These curves were subsequently used to calculate mean values of peak concentration, time for onset of peak, and area under the serum curve, as well as a mean serum curve for a study group.

RESULTS

Absorption in fasting and nonfasting subjects. Results given in Table 1 show serum levels and urinary excretions of ampicillin recorded after oral administration of pivampicillin in single doses equimolar to 250 mg of

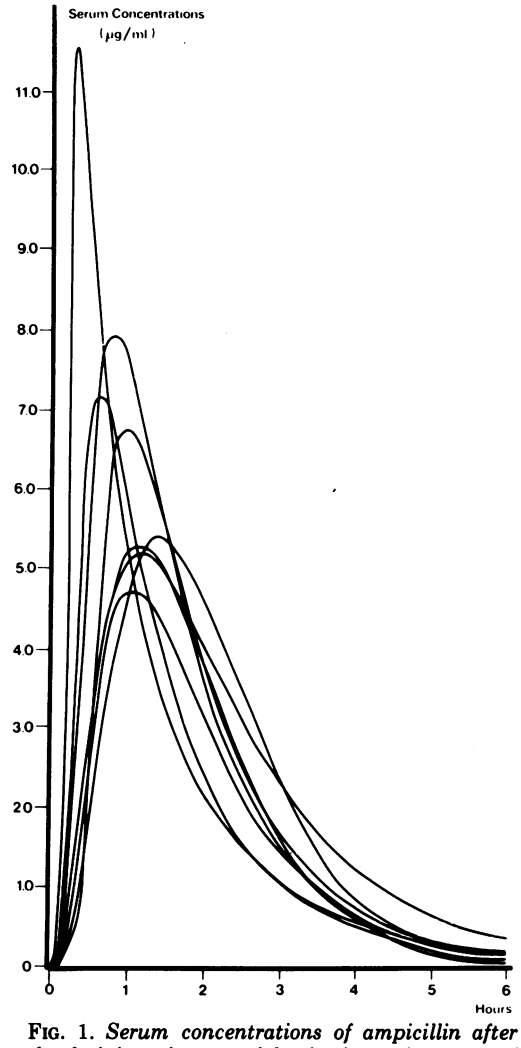

FIG. 1. *Serum concentrations of ampicillin after oral administration, to eight fasting volunteers, of pivampicillin hydrochloride equimolar to 250 mg of ampicillin. The curves are based upon data given in Table 1.*

ampicillin to a group of healthy volunteers in the fasting state or immediately after a standard breakfast. Individual serum curves are presented in Fig. 1 and 2, and mean curves are compared in Fig. 5.

The individual serum curves for the two absorptive states showed similar variations in shape and distribution indicating the same absorption pattern in both fasting and nonfasting subjects. Postprandial ingestion of pivampicillin produced practically the same maximal concentration, but it occurred a little later, corresponding to the slightly delayed ascension of the serum curve (see Fig. 5). When food was given, the mean curve peaked with 6.6 μg/ml at 1 h 12 min after the dosing, whereas the maximum averaged 6.8 μg/ml at 56 min in fasting subjects (see Table 4).

The total bioavailability, as represented by the area under the serum curve, was slightly improved by the presence of food in the stomach. The mean area was 12.8 in fasting and 14.2 in nonfasting subjects.

The urinary excretion of ampicillin during the first 6 h after administration was slightly reduced by postprandial ingestion, corresponding to the slight delay in absorption indicated by the course of the serum curve (see Fig. 5). The recovery averaged 73 and 67% in fasting and nonfasting subjects, respectively.

Comparison with ampicillin: (i) capsules.

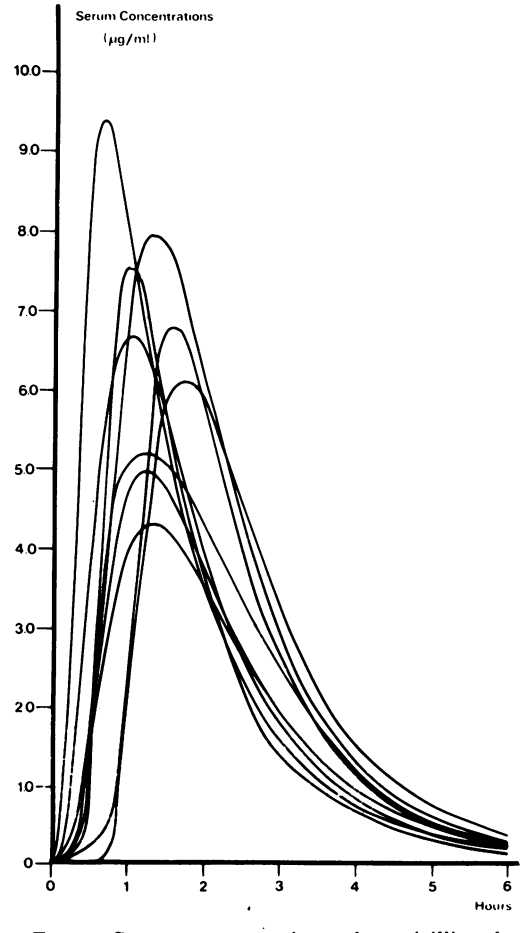

FIG. 2. *Serum concentrations of ampicillin after oral administration, to nine volunteers immediately after a meal, of pivampicillin hydrochloride equimolar to 250 mg of ampicillin. The curves are based upon data given in Table 1.*

TABLE 2. *Serum concentrations and urinary excretion after oral administration of single doses of ampicillin to healthy fasting volunteers*

Dose (mg)	Serum concn (μg/ml)								Urinary excretion[a] (% of dose)
	0.25[b]	0.5	1	1.5	2	3	4	6	
250	0.20	0.67	1.3	0.96	1.0	0.96	0.65	0.35	22
	0.03	0.17	1.3	2.3	2.2	0.96	0.43	0.09	27
	<0.03	0.43	1.3	1.3	0.81	0.46	0.37	0.08	17
	<0.03	0.39	1.4	1.3	1.1	1.0	0.30	0.07	18
	<0.03	0.17	1.4	2.2	1.7	1.8	0.87	0.16	53
	0.07	0.74	1.9	1.7	2.8	1.3	0.77	0.17	40
	<0.03	0.24	1.7	2.3	2.1	0.83	0.40	0.11	25
	<0.03	0.74	1.8	1.7	1.5	1.2	0.62	0.10	29
									Mean: 29
500	0.03	0.36	1.7	2.6	3.3	2.1	2.0	1.3	25
	<0.03	<0.03	0.75	3.2	4.9	3.2	2.2	0.69	39
	<0.03	0.47	1.7	1.8	1.6	1.4	1.7	0.76	15
	<0.03	0.80	1.9	2.2	2.1	1.5	0.77	0.23	16
	<0.03	0.06	0.78	1.4	2.5	2.4	1.3	0.42	19
	0.09	1.9	3.8	4.6	4.1	2.3	1.1	0.36	25
	<0.03	0.44	3.5	4.0	4.3	2.5	1.6	0.61	32
	<0.03	0.71	2.7	3.0	3.4	1.8	0.77	0.18	28
									Mean: 25

[a] 0 to 6 h after administration.
[b] Hours after administration.

TABLE 3. *Mean values of maximal concentration of ampicillin in serum (C_{max}), the time for its occurrence (T_{max}), and area under the serum curve (A) after administration of single oral doses of pivampicillin and ampicillin*

Drug	Dose (mg of ampicillin)	Absorptive state	C_{max} (μg/ml)	T_{max} (h)	A (μg/ml × h)
Pivampicillin	250	Fasting	6.8	0.94 (56 min)	12.8
Pivampicillin	250	Postprandial	6.6	1.2 (1 h 12 min)	14.2
Ampicillin	250	Fasting	1.96	1.4 (1 h 24 min)	5.4
Ampicillin	500	Fasting	3.2	1.7 (1 h 42 min)	11.6

For comparison, studies on ampicillin administered to fasting subjects were performed with the same group of volunteers. The drug was administered in 250- and 500-mg capsules. Results of serum concentrations and urinary recoveries of the drug are shown in Tables 2 and 3, respectively. Individual serum curves are presented in Fig. 3 and 4, and mean curves are compared in Fig. 5 with curves for pivampicillin administered orally in an amount equimolar to 250 mg of ampicillin to fasting and nonfasting subjects.

Considerably higher serum concentrations of ampicillin were obtained with pivampicillin than with the parent drug. The average peak concentration after pivampicillin treatment was three times higher than after the equimolar dose of ampicillin and two times higher than after twice the equimolar dose. In addition to being higher, the maximum tended to occur earlier after administration of pivampicillin also when given with food (Table 3).

For both drugs, the distribution of the individual curves (Fig. 1 through 4) indicates a variation in absorption among individuals, but only the best individual curves for a 500-mg ampicillin dose reach a maximum similar to that of the lowest curve for the pivampicillin dose corresponding to 250 mg of ampicillin.

The areas under the mean serum curves (Table 3) indicate that the bioavailability after pivampicillin administration is twice that obtained with an equimolar amount of ampicillin. The superior absorption of pivampicillin was also reflected in the urinary excretion of ampicillin, in which the two pivampicillin studies averaged 67 to 73%, whereas only 25 to 29% of the administered doses of ampicillin was recovered in the urine.

(ii) Suspensions. Oral suspensions of am-

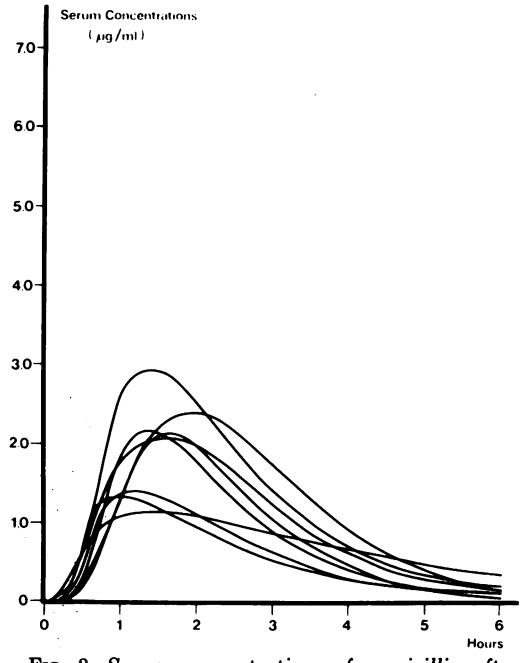

FIG. 3. *Serum concentrations of ampicillin after oral administration, to eight fasting volunteers, of ampicillin trihydrate equimolar to 250 mg of ampicillin. The curves are based upon data given in Table 2.*

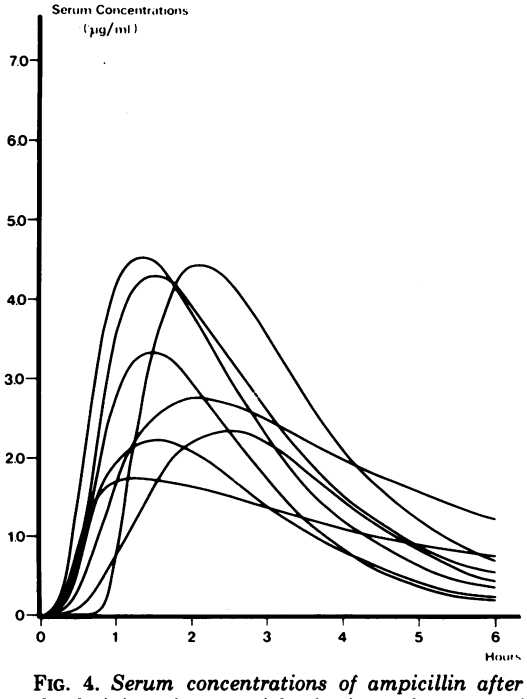

FIG. 4. *Serum concentrations of ampicillin after oral administration, to eight fasting volunteers, of ampicillin trihydrate equimolar to 500 mg of ampicillin. The curves are based upon data given in Table 2.*

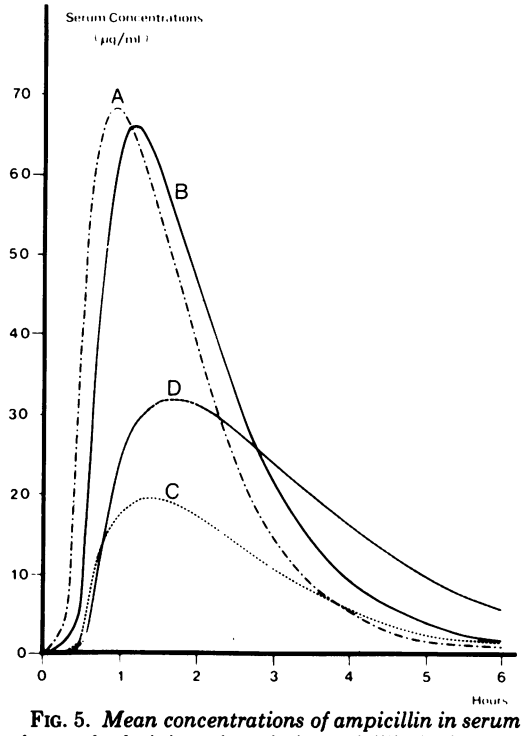

FIG. 5. *Mean concentrations of ampicillin in serum after oral administration of pivampicillin hydrochloride equimolar to 250 mg of ampicillin to volunteers in the fasting state (A) or immediately after a meal (B), and administration of ampicillin trihydrate equimolar to 250 (C) and 500 (D) mg of ampicillin to fasting volunteers. Individual curves are presented in Fig. 1 to 4; data are from Tables 1 and 2.*

picillin and pivampicillin were compared in another group of healthy volunteers. The medications were administered in amounts corresponding to 250 mg of ampicillin. Individual serum concentrations and urinary excretions resulting from these studies are shown in Table 4, and mean serum curves are compared in Fig. 6.

Serum levels recorded for the liquid dosage forms emphasize the difference noted for the solid dosage forms. The average maximal concentration was 7.7 μg/ml 40 min after administration of pivampicillin, and 2.6 μg/ml 1 h 30 min after administration of ampicillin. The areas under the mean serum curves were 14.3 and 7.9, respectively. The urinary excretion of ampicillin after pivampicillin administration was also, in this case, twice as high as for ampicillin; the percentage averaged 76 for pivampicillin and 37 for ampicillin during the first 6 h.

Effect of probenecid. Serum levels and urinary excretions of ampicillin determined in 10

TABLE 4. *Serum concentrations and urinary excretion of ampicillin after administration of single doses of oral suspensions of pivampicillin and ampicillin (equimolar to 250 mg of ampicillin) to healthy volunteers*

Drug	Serum conc (μg/ml)							Urinary excretion[a] (% of dose)
	0.25[b]	0.50	1	2	3	4	6	
Pivampicillin	1.3	2.8	5.9	4.1	2.5	0.96	0.30	80
	1.7	4.1	7.7	3.9	1.6	1.1	0.27	68
	3.6	5.3	6.4	2.5	1.1	0.45	0.14	82
	2.8	6.4	9.6	2.8	1.2	0.69	0.21	75
	5.4	5.8	7.7	3.3	2.1	0.81	0.23	91
	6.5	9.4	8.0	2.6	1.2	0.64	0.18	64
	3.4	8.7	5.5	1.7	0.96	0.48	0.12	67
	3.5	6.8	9.8	2.6	1.4	0.69	0.23	69
	1.6	7.4	11	3.7	1.7	0.96	0.24	90
	3.7	8.7	7.3	3.1	1.3	0.61	0.21	76
								Mean: 76
Ampicillin	0.30	1.0	2.9	2.0	1.2	0.49	0.09	41
	0.59	1.7	2.3	1.5	1.8	1.6	0.63	44
	0.18	0.71	1.1	0.96	0.57	0.36	0.06	20
	0.14	0.51	1.4	2.8	2.6	1.7	0.58	46
	0.40	1.4	2.6	3.1	2.1	1.2	0.28	45
	0.24	0.96	2.6	1.8	1.1	0.46	0.14	23
	<0.04	0.33	1.5	1.6	1.0	0.96	0.17	38
	0.47	1.5	2.8	2.9	1.2	0.77	0.14	47
	0.68	2.1	5.0	3.0	1.6	1.4	0.30	35
	0.41	1.1	2.4	1.6	0.64	0.29	0.06	32
								Mean: 37

[a] 0 to 6 hours after administration.
[b] Hours after administration.

fasting subjects after single oral 1,400-mg doses of pivampicillin alone or in combination with 1000 mg of probenecid are shown in Table 5, and mean serum curves are presented in Fig. 7.

Higher and more prolonged serum levels were obtained after administration of probenecid. The average maximal serum concentration was increased from 18.3 to 21.7 μg/ml, and significantly higher concentrations were maintained during the remaining period. The area under the serum curve was increased from 50.2 to 76.8.

The maintenance of high serum levels indicates a retarded elimination. This was confirmed by a reduction in the mean urinary excretion of ampicillin over the 0- to 6-h period, 68% when pivampicillin was given alone and 59% in the presence of probenecid. After 24 h, the corresponding figures were 72 and 66%, respectively.

DISCUSSION

The data in this paper have confirmed that pivampicillin is absorbed more efficiently from the gastrointestinal tract than is ampicillin. Compared with ampicillin given orally, pivampicillin gave rise to earlier and considerably higher peak concentrations as well as improved bioavailability. At a dose level equimolar to 250 mg of ampicillin, the maximal serum concentration produced by pivampicillin was three times higher than that seen after ampicillin administration, which is in agreement with the ratios mentioned previously (2, 7, 9, 10, 16). Furthermore, the peak concentration for pivampicillin at the 250-mg dose level was twice the maximum obtained for a 500-mg ampicillin dose. The overall bioavailability, as determined by the area under the serum curve, was doubled with pivampicillin when compared with an equimolar dose of oral ampicillin. Even when compared with twice the equimolar dose of ampicillin, the area under the curve was greater with pivampicillin. The urinary recovery of ampicillin, which was found to be twice as high for pivampicillin as for ampicillin administered orally, agreed with the results of other investigations (2, 7, 10, 21) and emphasized the superior absorption of pivampicillin. Moreover, the excretion of ampicillin in urine after oral pivampicillin administration corresponds to the recovery after an intramuscular injection of ampicillin (10, 14) and, as pointed out by Jordan et al. (10), indicates practically complete absorption of pivampicillin from the gastrointestinal tract. For oral ampicillin, the urinary recovery is approximately half that obtained after intramuscular administration in the studies of Kunin (14) and Kirby and Kind (11).

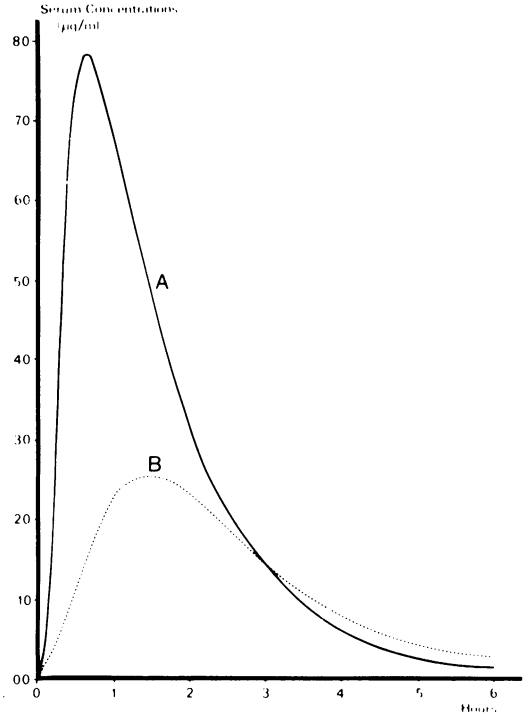

FIG. 6. *Mean concentrations of ampicillin in serum of 10 volunteers after administration of oral suspensions of pivampicillin (A) and ampicillin trihydrate (B) in doses equimolar to 250 mg of ampicillin. The curves are based upon the data given in Table 4.*

Results obtained for the liquid dosage forms showed improved absorption for both drugs as compared to the solid dosage forms, but the difference between the two suspensions with respect to serum levels and urinary excretions was similar to the differences between the solid dosage forms. The absorption of pivampicillin was not significantly affected by concurrent administration of food. These results were very similar to those reported by Foltz et al. (7), who found that food tended to cause a slight delay in absorption and a minor enhancement of the total bioavailability. Magni and Sjövall (15) reported an impairing effect by food for both pivampicillin and ampicillin, but their conclusions were based on conflicting figures. Although the differences in serum levels might indicate a diminished absorption of both drugs, another conclusion could be drawn from the urine data. For ampicillin the reduction in urinary excretion after ingestion of food agreed perfectly with the decreased serum levels, both indicating an incomplete absorption. For pivampicillin, however, the urinary excretions measured by Magni and Sjövall were very much the same, indicating that the absorption of this

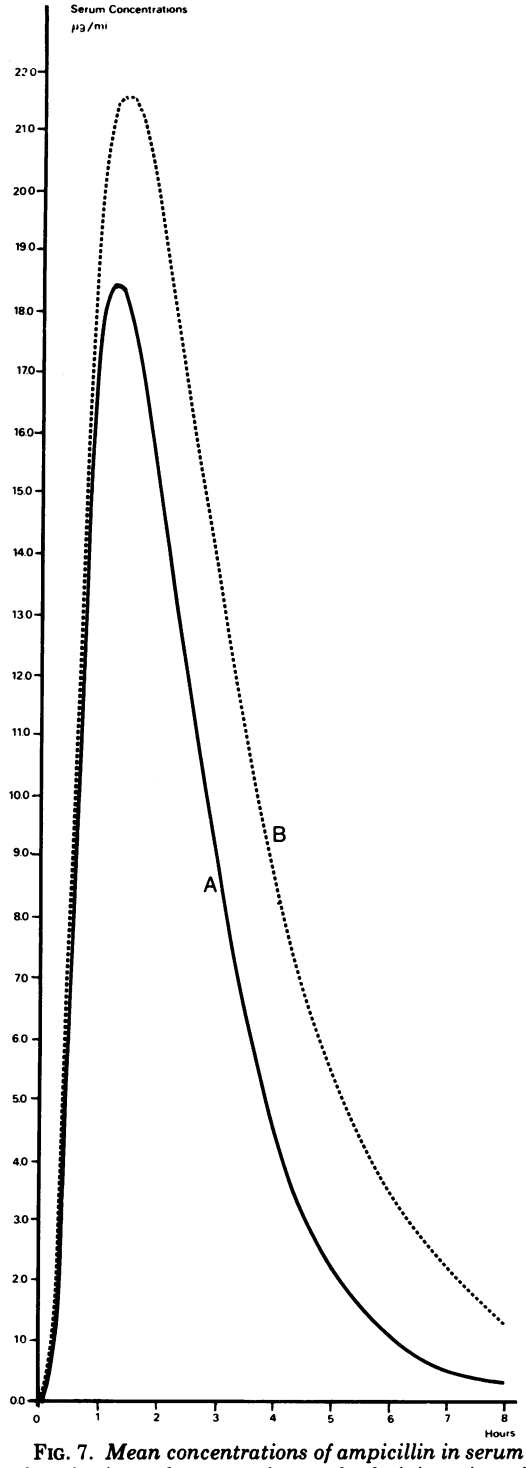

FIG. 7. *Mean concentrations of ampicillin in serum of 10 fasting volunteers after oral administration of pivampicillin hydrochloride equimolar to 1,000 mg of ampicillin alone (A) or with 1,000 mg of probenecid (B). The curves are based upon the data given in Table 5.*

TABLE 5. *Serum concentrations and urinary excretion of ampicillin after administration to healthy volunteers of single oral doses of pivampicillin hydrochloride (equimolar to 1,000 mg of ampicillin) alone or in combination with 1,000 mg of probenecid*

Dose regimen	Serum concn (μg/ml)								Urinary excretion (% of dose)	
	0.25[a]	0.50	1	2	4	6	7	8	0–6	0–24
Without probenecid	0.65	10	17	18	4.7	0.96	0.96	0.44	76	76
	1.0	13	19	17	4.7	0.87	0.35	0.33	92	95
	0.11	4.1	14	16	3.7	0.87	0.74	0.31	97	100
	1.5	8.9	14	17	4.9	0.87	0.54	0.30	68	76
	0.66	3.0	9.7	16	9.9	4.4	3.0	1.3	72	81
	3.1	16	20	7.7	1.2	0.43	0.23	0.15	47	48
	1.1	2.3	11	16	7.2	1.8	1.1	0.67	50	54
	1.3	16	23	16	3.1	0.96	0.56	0.31	47	49
	0.67	6.0	14	11	4.8	0.96	0.56	0.28	65	69
	0.56	7.6	20	16	2.0	0.64	0.35	0.22	70	70
									Mean: 68	Mean: 72
With probenecid	2.0	12	23	23	7.9	4.4	4.0	1.7	64	69
	<0.04	2.3	18	17	13	3.6	2.8	1.2	68	74
	2.8	7.8	14	27	4.9	1.9	1.8	0.66	66	70
	<0.04	0.87	18	24	17	4.9	4.5	2.6	57	67
	0.64	7.0	22	23	9.4	3.4	2.3	1.0	80	85
	0.87	8.1	20	10	3.7	1.4	1.0	0.52	39	42
	0.81	7.3	18	15	7.9	3.6	2.1	1.7	56	62
	2.6	13	31	22	12	5.0	3.6	2.6	55	66
	<0.04	1.0	9.6	13	7.1	2.1	1.2	0.65	50	60
	0.26	5.8	20	17	6.4	3.0	2.1	1.6	50	61
									Mean: 59	Mean: 66

[a] Hours after administration.

drug was practically unaffected by ingestion of food. Fernandez et al. (6) also reported decreased serum levels after postprandial administration of pivampicillin, whereas their data for the urinary excretion showed that the effect of food on the absorption of pivampicillin was almost insignificant. The overall conclusion must be that the absorption of pivampicillin is not significantly influenced by administration of food.

In agreement with the results obtained by Simon et al. (21), administration of probenecid concurrently with pivampicillin caused higher and prolonged concentrations of ampicillin in the serum. This was to be expected from the known effect of probenecid on the tubular excretion of antibiotics. The fact that pivampicillin produces peak levels two to three times higher than an equimolar dose of oral ampicillin, as well as the double overall bioavailability, means that a 350-mg dose of pivampicillin, although chemically equivalent to 250 mg of ampicillin, is therapeutically equivalent to a 500-mg dose of ampicillin. Furthermore, since the absorption of pivampicillin is practically unaffected by the presence of food in the stomach, patients can benefit from the comfort of receiving their medication with a meal without loss of therapeutic effect.

LITERATURE CITED

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